DAIDS INDEPENDENT SAFETY MONITOR (ISM) GUIDELINES

1. ROLES AND RESPONSIBILITIES

An Independent Safety Monitor (ISM) is a physician or other health-care professional with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This may be accomplished by review of individual serious adverse event reports immediately after they occur and/or review of periodic cumulative safety monitoring reports. Based on review of this safety data, the ISM makes recommendations regarding the safe continuation of the study.

An ISM could be the sole independent monitor for the study or may perform this role as a member of a Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC). An ISM is appropriate as the sole independent safety monitor for small, early phase studies, such as some pharmacokinetics, proof-of-concept, or immunogenicity studies, or other studies of short duration. For some Phase I studies, an ISM may work with the protocol team (and particularly with the NIAID MO/MM) in review of safety data/reports, including both individual case AE data and periodic cumulative AE reports.

DSMBs and SMCs should consider the need to designate one or more members as ISM(s). In the case of SMCs and DSMBs, the ISM focus may be directed at review of serious adverse events (SAE) reports and/or review of periodic cumulative AE reports that are generated between scheduled interim full committee reviews. The contents and schedule of reports to be reviewed by the ISM will be specified in the Study Data Monitoring Plan (SDMP) with additional input from the SMC or DSMB.

If the ISM is the sole independent reviewer for a study (not a DSMB or SMC member) NIAID may retain the responsibility to identify the ISM and define his/her role. In some cases, NIAID may delegate this responsibility to the study PI. If delegated, the CVs of the persons(s) proposed to serve as the ISM and a detailed description of his/her role of the ISM must be submitted to DAIDS at least 30 days before the projected date of study initiation. DAIDS must give written approval of the ISM and role before study initiation.

2. SELECTION AND INVITATION TO PARTICIPATE

The ISM is selected based on relevant study-related expertise. Participation is usually for the duration of the study. He/she may be a member of a participating institution's staff. The ISM cannot be under the direct supervision of an investigator and should preferably be from a different organizational group.

Conflict of Interest

An ISM cannot have any other involvement in the conduct of the study. Furthermore, no ISM may have financial, proprietary, professional, or other interests that could affect impartial, independent decision-making. Letters of invitation to prospective ISMs should include the following: "Acceptance of this invitation to serve as the ISM for this study

confirms that I do not have any financial or other interest with any of the collaborating or competing pharmaceutical firms or other organizations involved in the study that constitute a potential conflict of interest." In addition, all ISMs will sign a Conflict of Interest certification to that effect at the time they are asked to participate (see Attachment 1).

If the ISM performs this role as a member of a DSMB or SMC, the NIAID program staff or the DSMB or SMC Chair (as appropriate) will reconfirm that no conflict of interest exists for the ISM at the beginning of every DSMB or SMC meeting. Interests that may create a potential conflict of interest must be disclosed to the DSMB or SMC prior to any discussion. The DSMB or SMC will determine how to handle such potential conflict. The DSMB or SMC can require that an ISM with a potential conflict not vote or take other means deemed appropriate.

If the ISM is acting as the sole independent monitor, the NIAID Program/Project Officer (PO) will reconfirm at least annually that no conflict of interest exists. Interests that may create a potential conflict of interest must be disclosed to the NIAID PO prior to any review of data. The NIAID PO, in consultation with their Branch Chief, Division Director, or other appropriate staff, will determine if the relationship is in conflict or gives the appearance of a conflict such that the individual should not serve as the ISM. NIAID can require that an ISM with a potential conflict not vote or take other means deemed appropriate. NIAID may dismiss an ISM in the event of unmanageable potential conflict.

3. STUDY MATERIALS FOR ISM REVIEW

The primary focus of the ISM is to independently review selected safety data as determined by the SDMP and/or as guided by the SMC/DSMB. This may include thorough evaluation of some or all individual serious adverse events and/or review of periodic cumulative adverse event reports. Particularly as the sole monitor, the ISM may evaluate serious adverse events against the known safety profile of the study product. Clinical and laboratory data, clinical records, and other study-related records should be made available for ISM review. If necessary, special reports are prepared by the investigator or study statistician.

It is the responsibility of the PI to ensure that the ISM is informed of all new safety information relevant to the study product. This includes providing the ISM with a copy of the current Clinical Investigator's Brochure (CIB) before study initiation as well as promptly providing all CIB revisions and all safety reports issued by the sponsor. Summary safety and enrollment data should be forwarded periodically to the ISM. The ISM should receive all protocol revisions and may receive other documents relating to the study.

4. REPORTS FROM THE ISM

The following reports are submitted by the ISM when acting as the sole independent monitor (otherwise the ISM operates under the guidelines of the DSMB or SMC).

4.1 Review Report

According to pre-specified criteria delineated in the SDMP and/or by the SMC/DSMB, and as needed in response to study developments, the ISM will communicate in writing a summary of his/her findings, any concerns, and recommendations. Unless otherwise specified, the ISM will submit the report to the NIAID PO. The NIAID PO will forward the summary report to a designated study team representative (usually the Principal Investigator), SMC or DSMB members and to other designated NIAID staff. The study team representative is responsible for disseminating the ISM summary report to any other site investigators and each investigator must, in turn, submit the report as per local IRB/EC policy. If under an IND, the sponsor is responsible for submitting the summary report to the FDA and to any industrial collaborators as appropriate.

4.2 Immediate Action Report

The ISM will notify the NIAID PO of any findings of a serious and immediate nature including any recommendations to significantly modify or discontinue all or part of the trial. In addition to verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed to NIAID in writing within one day of the ISM review. This written, confidential report may contain unmasked supporting data and include the ISM's rationale for the recommendations. The report will be submitted to the NIAID PO, who will determine furter distribution. If the study is under an NIAID IND, NIAID will forward the report to the FDA as needed.

4.3 Dual Role Reporting

When an ISM is an SMC or DSMB member, the ISM recommendations concerning continuation or major changes in study conduct will be made to the SMC or DSMB. When the ISM is the sole independent monitor, such recommendations will be made directly to the NIAID PO. In all cases, final decisions regarding these recommendations will be made by NIAID.

Attachment 1

CONFLICT OF INTEREST CERTIFICATION
FOR INDEPENDENT SAFETY MONITOR (ISM)
NOTE: DO NOT USE FOR DSMB, SMC

Confidential

ISM for the ABC Trial on XYZ

I have not been within the past 12 months a part-time, full-time, paid, or unpaid employee of or am not presently negotiating for employment with any organizations that are: (a) involved in the studies under review; (b) whose products or services will be used or tested in the studies under review, or (c) whose products or services would be directly and predictably affected by any outcome of these studies;

- I am not an officer, member, owner, trustee, director, expert advisor, or consultant, i.e., speaker, researcher, contractor, grantee or collaborator, of such organizations;

- I do not have any financial interests or assets that exceed $10,000 in any organizations meeting the above criteria, nor do my spouse or dependent children or domestic partner;

- I do not have any intellectual, proprietary interest in any of the products being reviewed or in products in direct competition with such products; and,

- I have not been involved in any litigation regarding these organizations (e.g., plaintiff, defendant, expert witness).

PLEASE COMPLETE BELOW.

☐ No relevant interests or activities.
☐ I will disclose exception(s) to the DSMB or SMC (as appropriate) prior to any discussion so that they can be reflected in the minutes along with the DSMB's determination as to how to handle such exception(s). If acting as the sole monitor, I will disclose exception(s) to the NIAID Program/Project Officer prior to review of data so that they can be reflected in the review report along with NIAID's determination as to how to handle such exception(s).

I will notify the NIAID Program/Project Officer promptly if a change occurs in any interests or activities during the tenure of my responsibilities.

I am aware of my responsibilities for maintaining the confidentiality of any non-public information that I receive or become aware of through this activity, and for avoiding using such information for my personal benefit, the benefit of my associates, or the benefit of organizations with which I am connected or with which I have a financial involvement.

_____	_____	_____
ISM's name (please print)	Signature	Date